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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/888,057	07/03/97	STICE S	000270-012

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EXAMINER	
CROUCH, D	
ART UNIT	**PAPER NUMBER**
1632	11

DATE MAILED: 08/04/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/888,057	Stice et al.
Examiner	**Group Art Unit**
Deborah Crouch	1632

☒ Responsive to communication(s) filed on *May 24, 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-78* is/are pending in the application.

Of the above, claim(s) *36-45, 66-70, and 77* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-35, 46-65, 71-76, and 78* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Applicant's election without traverse of group I in Paper No. 10 is acknowledged.

Claims 1-35,46-65,71-76 and 78 are examined in this office action.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-17,24,25,61 and 63 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 103-126 of allowed of U.S. Patent No. 08/781,752 Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are obvious over the claims of '752. The instant claims are methods of cloning pigs and methods of cloning transgenic pigs. The claims of '752 are to methods of cloning mammals and methods of cloning transgenic mammals, with a specific claims to pig. Thus the instant claims are obvious over the claims of '752 as the ordinary artisan having claims 103-126 would have sufficient teachings and motivation to produce the cloned pigs as instantly claimed.

These are provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-17,24,25,29,30,32,34,46-48,50,52,54,55,57,59,61-63 and 78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of cloning a pig comprising inserting a differentiated pig cell or cell nucleus, a differentiated pig cell or cell nucleus wherein a DNA sequence is inserted, removed or modified, a pig CICM cell or cell nucleus, into an enucleated mammalian oocyte, activating the nuclear transfer unit, culturing the activated nuclear transfer unit to greater than the 2-cell stage and transferring the cultured nuclear transfer unit to a host mammal, a method of producing a CICM cell line comprising inserting a differentiated pig cell or cell nucleus, or a differentiated pig cell or cell nucleus wherein a DNA sequence is inserted, removed or modified, into an enucleated mammalian oocyte, activating the nuclear transfer unit, culturing the activated nuclear transfer unit to greater than the 2-cell stage and culturing cells obtained from the nuclear transfer unit, a method of producing a pharmaceutically active protein expressing a transgenic pig offspring, and methods of making chimeric pigs.

The claims are not enabled as the specification does not provide sufficient guidance on cloning pigs, cloning transgenic pigs, methods of making a pharmaceutically active protein or methods of making chimeric pigs by the methods claimed such the artisan could repeat the method and have a reasonable expectation of success. The nature of the art at the time of filing was that the cloning of a pig, that is the production of a fully, developed pig from a fully differentiated pig cell or from a nucleus of a fully differentiated pig cell was unlikely to be successful. At the time of filing, the art knew that the transfer of nuclei from differentiated adult cells into frog oocyte would result in the production of tadpoles, but not the differentiation to adult frogs (Wilmut et al, page 810, col. 2, parag. 2, lines 1-3). The art, however, had reported the development of mammals by the insertion of a nucleus from a totipotent embryonic cells into

an enucleated oocyte (US Patent 4,994,384, col. 10, lines 4-10; Sims et al, page 6146, col. 2, parag. 1-3 and Campbell et al, page 65, col. 2, lines 3-11). Thus the artisan while being able at the time of filing to obtain guidance from the art on the production of mammals by the insertion of a nucleus from a totipotent embryonic cell into an enucleated oocyte, the artisan could not have found such guidance when the nucleus was from a fully differentiated cell. For this the artisan could only rely on the instant specification.

The specification provides working examples to show the development of chimeric an transgenic bovine embryos and fetuses, but no production of a live birth. Example 1 demonstrates the production of fibroblast cultures from fetal bovine and porcine tissues and from adult bovine tissue. Cells from each of these cultures were shown to take up and express the β-galactosidase gene. One cell line, CL-1, a fetal bovine fibroblast cell line, provided the donor nucleus for nuclear transfer experiments where transgenic fetal bovines. Example 2 demonstrates the production of CICM cells first producing a nuclear transfer unit by inserting the nucleus of a bovine fetal fibroblast (CL-1) into an enucleated oocyte and culturing the nuclear transfer unit . Disaggregation of the cultured NT's resulted in CICM cultures. Intact CICM cells were inserted into 8-16 cell embryos to produce chimeric fetal calves. Transgenic fetal calves were produced by removing the nucleus of a CICM cell and inserting it into an enucleated oocyte, as was done in example 1 with fetal fibroblasts. However none of these examples demonstrate the live birth of a pig, a transgenic pig, or a chimeric pig. There is no evidence to support the production of pig embryos with isolation and culture of the inner cell mass cells. In addition, there is no showing that expression of the transgene would be sufficient to produce a pharmaceutically active protein. This remains unpredictable, as even the more established methods where totipotent embryonic cell nuclei were used resulted in the loss of mammals during gestation (Campbell et al, page 65, col. 2, lines 5-10). Even post-filing art, employing a

method similar to applicant's resulted in the birth of only one sheep, further demonstrating the unpredictability of the claimed method (Wilmut et al, page 812).

The production of chimeric animals is of itself lacking reproducibility. There are not guidelines provided in the specification for the production of a chimeric mammal such that the mammal has a use to the art. Chimeric mammals are unpredictable, as the contribution of the transferred cell or nucleus is not controllable. There is no method for regulating those portions of the mammal to which the transferred cell or nucleus contributes, nor is there a method for reproducibly making chimeric mammals that are the same. For example is mammal 1, the transferred cell or nucleus may contribute to the liver, and in mammal 2, it may contribute to the brain. There is no way to reproducibly ensure that the transferred cell or nucleus contributes the same in multiple mammals. Thus the production of chimeric mammals is unpredictable.

Further, there is no evidence of record that the transgenic or chimeric fetuses and mammals produced by the instantly disclosed method would result in mammal that would provide organs for transplantation. The transgene would need to be expressed sufficiently so that the organ would be immune from rejection for example. The showing of β-galactosidase expression is not sufficient to demonstrate transgene expression sufficient for transplantation. There is no correlation in the art or in the specification between levels of β-galactosidase expression and levels of transgene expression in general that affords a new use to mammalian embryos, fetuses, offspring or progeny. The specification at page 10, lines 9-21 and page 11, lines 7-18 discusses the uses of the mammals as organ donors. It is not clear how a mammal that does not express a transgene that alters the host-graft response will be useful as an organ donor. As for other uses, the specification fails to disclose other clear uses for the mammals and none are apparent. There is no evidence that the mammals made by the disclosed methods provide a patentable use. The question here is how would the artisan use the mammals made by the method?

The unpredictability of the method as a whole lies in the need to convert a differentiated cell to a totipotent cells. As cells contain the same DNA complement. However, in differentiated tissues, not all DNA sequences are expressed. For example, a liver does not make rhodopsin and retinal cell structures, and retinal cells do not make clotting factors and hepatocyte structures. For a cell to go through all the steps of development it, or its nucleus, must be reverted back to the stage where all DNA sequences can potentially be expressed, and expression regulated according to developmental stage. Applicant has not shown that the method of cloning using transferred cell or nucleus demonstrated is sufficient for the production of fully developed mammals. The examples show the production of transgenic and chimeric bovine fetuses, but there is no demonstration that the activation method would active non-bovine nuclei. Further, the gene activation time for mammalian embryos may be critical for producing a fully differentiated mammal. Activation times were known in the art to vary: the mouse activates at the 2-cell stage, and human; cow and sheep activate around the 4 to 8 cell stage (Schultz et al, page 206, col. 2, parag. 2, lines 1-3). The activation time may be critical for the production of a fully developed pig.

Further, applicant is not enabled for transferring the NT unit to a host mammal. The placenta for all mammals is made from embryonic tissue. The implantation of a pig NT unit into a sheep for example, would result in an immune response being initiated by the host ewe that would result in a loss of the pig embryo or fetus. For this reason, applicant, once overcoming the rejections above, would only be limited to transfer of the pig NT unit into a host sow.

As the production of an CICM cell line would require, by applicant's claim, first the production of a pig embryo by the claimed methods, the method of producing a pig embryo would need to be enabled. Once enablement of the embryo is enabled, the method of producing a CICM cell line would be enabled as the inner cell mass comes from the embryos and can be

produced by methods already known in the art from producing CICM cell lines from embryos produced by other methods.

Applicant is not enabled for methods of producing a pharmaceutically active protein which is isolated from a transgenic pig offspring, or the isolation of such a protein from milk of the pig. There is no evidence of record that a pig produced by the method of cloning claims would express a protein sufficiently in any of its tissues or organs sufficiently to produce a proteins of any type. The phrase "pharmaceutically active" further implies that the protein would be effective in treating a disease or condition. There is no evidence that the transgene expression obtained would be sufficient either for isolation or pharmaceutical purposes. The art at the time of filing taught that transgenic express was unpredictable without an undue amount of experimentation. At the time of filing, the choices of promoter/enhancer and other regulatory sequences, as well as the insertion site of the transgene into the genome of the animal was considered unpredictable. Transgenic animals were regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappell et al (1992) Current Opinion in Biotechnology 3, 549, col. 2, parag. 2). Additionally, "the position effect" and unidentified control elements also were recognized to cause aberrant expression (Wall (1996) Theriogenology 45, 61, parag. 2, line 9 to page 62, line 3). The elements of the particular construct used to make transgenic animals were held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) Journal of Biotechnology, constructs, page 275, col. 1, parag. 1).

As for claims to methods of producing an CICM cell line, methods of producing an CICM cell line that has a desired DNA inserted, removed or modified, and methods of using the CICM cell line to produce a chimeric embryo or chimera by insertion of a CICM cell into a fertilized pig embryo is not enabled. For the methods of claims 29,47,48,50,52,54,55,57 and 59, the CICM cell

would need to have totipotency, such that the genetic contribution of the CICM cell line would pass through the germ line. At the time of filing, the art taught for pig no definitive totipotent ES cells had been produced. Mullins et al. disclosed that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (Mullins et al (1996) Journal of Clinical Investigation page S38, column 1, first paragraph). The totipotency for ES cell technology in many livestock species has not been demonstrated (Seamark (1994) Reproductive Fertility and Development, page 6, Abstract). The specification does not provide guidance to overcome these art teachings that methodology for pig ES cell production was not known at the time of filing. While applicant may have a new method of producing a inner cell mass culture, applicant has not provided any evidence that these cells contribute to the germline in any fashion. If the germline does not contain any contribution from the inner cells mass genome, it is not seen how these methods have an enabled use. These methods are outside the claims to methods of cloning a pig, but enter into the realm of embryo reconstitution with an embryonic cell. Furthermore, it is not seen as how the methods of making chimeras has a use in the art. Chimeras on their face are unpredictable as there is no methodology which assures the reproducibility of making any particular chimera with any particular phenotype. Chimerism is a happenstance whereby the pattern of contribution by the recipient embryo and donor CICM cell genomes can not be controlled or predictably reproduced. Reproducibility is a requirement for enablement. In this regard claims 29,47,48,50,52,54,55,57 and 59 to methods of producing an inner mass cell line which includes methods of producing chimeric embryos, fetuses, progeny and offspring are not seen as having an enabled use also because the production of a chimeric embryo, fetus, progeny and offspring is not seen as reproducible for any particular phenotype.

Claim 29,47,48,50,52,54,55,57,59 and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29,47,48,50,52,54,55,57 and 59 are confusing because claim 29 is written as a method of producing an CICM cell line. Claims 47,48,50,52,54,55,57 and 59 read as if they are methods of producing chimeric embryos, fetuses, progeny and offspring. In particular, chimeric fetuses, progeny and offspring do not have the embryonic structure of an inner cell mass. Applicant should re-write claims 47,48,50,52,54,55,57 and 59 as method of producing chimeric embryos, fetuses, progeny and offspring.

Claim 78 lacks antecedent basis to claim 45. Claim 78 is to a method where a pharmaceutically active protein is isolated from the milk of the transgenic offspring. These concepts are not part of claim 45, which is to a method of therapy. It appears that claim 78 is meant to depend from claim 46, and is so examined in this office action.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19,20,27,28,65 and 71-75 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Cisneros et al (1996) J. Animal Science 74, 925-933.

The claims are drawn to pig offspring and progeny produced by claimed methods of cloning a mammal. However, as claims 19,20,27,28,65 and 71-75 are product by process claims, a teaching of the same products obtained by a different method serves as anticipatory art

against the instantly rejected claims. There is no language in claims 19,20,27,28,65 and 71-75 which provides any patentable distinction over the pig offspring and progeny in the art.

Cisneros et al teach a commercial pig breed, BCH, and a three breed cross, HYD, (page 926, col. 1, parag. 1, lines 4-6). These pigs inherently are progeny and offspring of parental crosses. Without a distinction which indicates a structural or functional difference between the claimed offspring and progeny and those disclosed in Cisneros et al, then Cisneros et al clearly anticipate the claimed invention.

Claims 18,26 and 64 are rejected under 35 U.S.C. 102(b) as being clearly anticipate by Cukrowska et al (1996) Immunology 87, 487-492.

The claims are drawn to pig fetuses produced by claimed methods of cloning a mammal. However, as claims 18,26 and 64 are product by process claims, a teaching of the same products obtained by a different method serves as anticipatory art against the instantly rejected claims. There is no language in claims 18,26 and 64 which provides any patentable distinction over the pig fetuses in the art.

Cukrowska et al teach Minnesota Miniature pig fetuses (page 488, col. 1, parag. 2, lines 1-3). The pig fetuses of claims 18,26 and 64 are not claimed to have a patentable distinction over the pig fetuses of Cukrowska et al. Therefore, Cukrowska et al clearly anticipate the claimed invention.

Claims 21-23 and 76 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Fodor et al (1994) Proced. Natl. Acad. Sci. 91, 11153-11157.

The claims are drawn to transgenic pig fetuses, offspring and progeny produced by claimed methods of cloning a pig. However, as claims 21-23 and 76 are product by process claims, a teaching of the same products obtained by a different method serves as anticipatory art against the instantly rejected claims.

Fodor et al teach the production of transgenic pigs which express a cDNA sequence encoding human CD59 (page 11155, figure 2). The pigs disclosed by Fodor et al are offspring and progeny of founder pigs (page 11154, col. 1, parag. 2, lines 2-4). As Fodor et al teaches the injection of the transgene into pig embryos, pig fetuses are inherent in the development to term pigs. Claims 21-23 and 76 do not distinguish from transgenic fetuses, offspring and progeny claimed from the fetuses, offspring and progeny taught by Fodor et al. Therefore, Fodor et al anticipate the claimed transgenic fetuses, offspring and progeny.

Claim 31 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Strojek et al 1990) Theriogenology 33, 901-913.

Claim 31 is drawn to a CICM cell line. However, as claim 31 is a product by process claim, a teaching of the same product obtained by a different method serves as anticipatory art against the claim.

Strojek et all teach the culture of ICM cells as cell lines 6-10 (page 903, parag. 5, lines 1-5 and page 907, figure 2). Claim 31 does not distinguish from the ICM cell line taught by Strojek et al. Without a distinction which indicates a structural or functional difference between the claimed cell line and that disclosed in Strojek et al, Strojek et al clearly anticipates the claimed invention.

Claim 35 is are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Brameld et al (1995) J. Endocrin. 146, 239-245.

Claim 35 is drawn to differentiated pigs cells made by a claimed process. However, as a product by process claim, a teaching of the same product by a different method serves as anticipatory art.

Brameld et al teaches differentiated pig hepatocytes (page 240, col. 1, parag. 2 to col. 2, through parag. 1). Claim 35 does not distinguish from the hepatocytes taught by Brameld et al. Without a distinction which indicates a structural or functional difference between the claimed

differentiated cells and those taught by Brameld et al, Brameld et al clearly anticipate the claimed invention.

Claims 49, 51 and 53 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Onishi et al (1994) Biology of Reproduction 51, 1069-1075.

Claims 49, 51 and 53 are drawn to chimeric pig embryos, fetuses, offspring and progeny. However, as product by process claims, a teaching of the same product by a different method serves as anticipatory art.

Onishi et al teach pig chimeras which result from crosses between Chinese pigs and European pigs (page 1071, figure 2). These pigs are chimeric offspring and progeny of the crosses. Pig chimeric embryos and fetuses are an inherent feature to teachings of chimeric pigs. As the claims do not provide a distinction over the chimeric pigs of Onishi et al, Onishi et al clearly anticipates the claimed invention.

Claims 56, 58 and 60 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Rosengard et al (1995) Transplantation 59, 1325-1333.

Claims 56, 58 and 60 are drawn to chimeric pig embryos, fetuses, offspring and progeny, where each has been so that a desired DNA sequence has been inserted, removed or modified. However, as product by process claims, a teaching of the same product by a different method serves as anticipatory art.

Rosengard et al teach pigs, which have had a desired DNA inserted, are germline mosaics for the DNA sequence encoding human DAF (page 1326, col. 1, parag. 1, lines 4-10). These pigs are deemed to be chimeric as some of the cells of pig contained the transgene and others did not. These mosaic/chimeric pigs are progeny and offspring of the embryo donors. As the mosaic/chimeric pigs are disclosed as beginning as microinjected embryos, transplanted into foster mothers, and allowed to develop to term, the claimed embryos and fetuses are inherent to

resultant pig. As the claims do not distinguish over the mosaic/chimeric pigs of Rosengard et al, Rosengard et al clearly anticipates the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner inwhich the invention was made.

Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Strojek et al (1990) Theriogenology 33, 901-913.

Claim 33 is drawn to a transgenic CICM cell line. However, as claim 33 is a product by process claim, a teaching of the same product obtained by a different method serves as anticipatory art against the claim.

Strojek et all teach the culture of ICM cells as cell lines 6-10 (page 903, parag. 5, lines 1-5 and page 907, figure 2). Strojek et al also teach that ICM cells can be transformed to provide a method for producing transgenic livestock since pronuclear injection of livestock embryos has lead only to limited successes (page 902, lines 5-11). Thus Strojek et al provide the teachings and motivation for the production of ICM cells transformed to comprises a DNA sequence of interest. There is no functional or structural difference between a cell isolated from a transgenic pig or a cell transformed to comprise a DNA sequence of interest in it genome. Thus it would have been obvious to the ordinary artisan at the time of the instant invention to produce ICM cells that comprised a DNA sequence of interest integrated into its genome. Strojek also teaches that methodology for so transforming totipotent cells was known in the art at the time of filing (page 902, parag. 1, lines 5-8).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The fax number is (703) 308-4242.

Deborah Crouch

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Dr. D. Crouch
July 31, 1999